THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR DOLUTEGRAVIR SODIUM 50 MG FILM COATED TABLETS

Version number 01, 03/01/2023

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1. Introduction

Hetero's Dolutegravir is a generic medicine of Tivicay 50 mg film-coated tablets (of ViiV Healthcare UK Limited, United Kingdom). The proposed product is a tablet that contains, as the active ingredient, dolutegravir sodium (hereinafter referred to as Dolutegravir), antiviral for systemic use. Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. MYLTEGA DT is approved in Tanzania for use in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age.

1.1 Product details

Registration number	TAN 21 HM 0404
Brand name	Dolutegravir
Generic name, strength and form	50 mg Dolutegravir (as sodium) Film Coated Tablets
ATC classification	J05AJ03, Antivirals for systemic use, other antivirals
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Hetero Labs Limited, Address: Hetero Coporate, 7-2-A2, Industrial Estates, Sanath Nagar, Hyderbad-500 018, Telangana, India
Local Technical Representative	Kas Medics Address: Umoja Complex, Plot No. 11, First Floor, Uf09 & Uf10, Vingunguti Industrial Area, Along Nyerere Road, adjacent to 10 Wes Commercial Complex, Dar es Salaam, Tanzania

1.2 Assessment procedure

The application for registration of Dolutegravir was submitted on 23/07/2021. The product underwent full assessment. Assessment was completed in 3(three) rounds of evaluation. Dolutegravir was registered on 09/10/2021.

1.3 Information for users

Visual description of the finished product	Pink, round, biconvex, film coated tablets debossed with 'H' on one side 'D13' on the other side
Primary packing material	30's count HDPE bottle
Secondary packing materials	A printed carton box
Shelf-life and storage condition	24 months, Do not store above 30°C. Protect from moisture
Route of administration	Oral
Therapeutic indications	Indicated in combination with other anti-retroviral medicinal products for the treatment of Human Immunodeficiency Virus (HIV) infected adults and adolescents above 12 years of age.

2. Labelling and product information

Summary of product characteristics

The SmPC included all the relevant information to ensure correct and safe use of the medicine by healthcare providers. The complete SmPC can be accessed here.

Package insert/leaflet

The package insert is confirmed to be derived from the SmPC and contains sufficient data for the end user. Since the product is POM that is intended for long term use, the package insert contains both full prescribing information as per SmPC and simplified information for patients.

Container labels

The product label information is presented in English. Details in the secondary pack label include:

Brand name: Dolutegravir

Composition: Dolutegravir sodium equivalent to dolutegravir 50 mg

Pack size: 30 tablets

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Do not store above 30°C. Protect from moisture

Manufacturers addresses: Hetero Labs Limited, Unit-V, TSIIC Formulation SEZ, S. No 439, 440,441 & 458, Polepally Village, Jadcherla, (Mandal), Mahaboob Nagar (District)-509301, Telangana State, India

Unique identifier: N/A

Special warnings/precautions or instructions for use: Read the package leaflet before use

The details of the primary pack include:

Brand name and strength: Dolutegravir

Manufacturing details: batch number, manufacturing date, expiry date

Name of manufacturer: Hetero Labs Limited, Unit-V

The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.

Mock labels are appended as annex I.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

Information on quality of the API was submitted in form of Full details.

General properties
Dolutegravir sodium API is non-compendia.

Molecular formula: $C_{20}H_{18}F_2N_3NaO_5$

Chemical names:

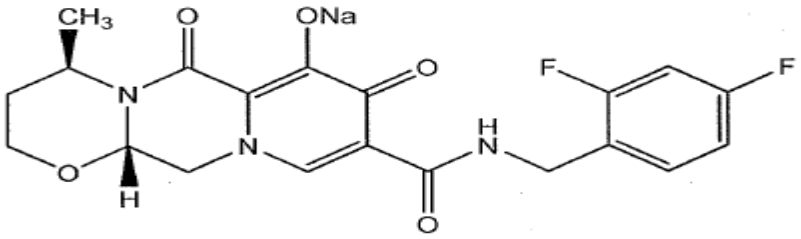
Sodium (4R,12aS)-N-[(2,4-Difluoro benzyl)carbamoyl] -4-methyl-6, 8-dioxo-3,4,6,8, 12,12a -hexahydro-2H-pyrido [l',2':4,5]pyrazino [2, 1-b] [1,3] oxazin-7-olate

Sodium (4R,12aS)-9-[(2,4-Difluoro benzyl)carbamoyl] -4-methyl-6, 8-dioxo-3,4 ,6,8, 12,12a -hexahydro-2H-pyrido [l',2':4,5]pyrazino [2, 1-b] [1,3] oxazin-7-olate

Sodium (4R, 12aS)-N-[(2,4-Di-fluorophenyl) methyl]-3,4,6,8,12,12a-hexa hydro-7-hydroxy-4-methyl-6,8-dioxo-2H-pyrido[1',2':4,5] pyrazino[2,1-b][1,3] oxazine -9-carboxamide

Sodium (4R, 9aS)-5-hydroxy-4-methyl-6,10-dioxo-3,4,6,9,9a,10-hexa hydro-2H-1-oxa-4a,8a-diazaanthracene-7-carboxylic acid 2,4-difluorobenzylamide

Structure:



Dolutegravir Sodium

Critical physico-chemical properties are:

Dolutegravir is a white to light yellow non-hygroscopic crystalline substance; it is slightly soluble in water, but practically not soluble over the physiological range. It presents 2 chiral centers and

pseudo-polymorphism. The most thermodynamically stable form is Form 1 (crystalline anhydrous). The manufacturer consistently produces the same polymorphic form.

Dolutegravir is classified as either BCS class II or IV molecule, therefore control of polymorphism and particle size is considered critical. The control of particle size distribution was demonstrated in the API specifications.

Manufacture

The API manufacturing site,

Name and address (including block(s)/unit(s))	**Responsibility**
Manufacturing site HETERO LABS LIMITED Hetero Labs Limited (Unit-I), Survey No.10, I.D.A. Gaddapotharam Village Jinnaram Mandal Sangareddy District-502 319 Telangana, INDIA. Contract manufacturing facility HONOUR LAB LIMITED Unit – III, Plot No. 4, Hetero Infrastructure Ltd., SEZ, N. Narasapuram Village, Nakkapalli Mandal, Visakhapatnam District – 531081, Andhra Pradesh, India.	Manufacturing, packaging, labelling, testing, storage

All manufacturers were noted to comply with WHO GMP requirements. Dolutegravir sodium API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per in-house standards and ICHQ3A. The parameters monitored during quality control are: description (visual), solubility, identification (IR, HPLC, and XRPD), sodium content, assay (HPLC), related substances (HPLC), diastereomer (HPLC), enantiomeric purity (HPLC), residual solvents (GC), water content (KF), particle size distribution (laser diffraction). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Dolutegravir sodium API is 60 months when packed in transparent polythene bags (purged with nitrogen), and outer black polythene bag and kept in HDPE drums with silica gel packers and stored at 25ºC, excursions permitted between 15ºC to 30ºC.

Quality of the Finished Pharmaceutical Product

Formulation

Dolutegravir is a pink, round, biconvex, film coated tablets debossed with 'H' on one side 'D13' on the other side.

Dolutegravir contains Dolutegravir sodium and other ingredients listed here after: microcrystalline cellulose, mannitol, sodium starch glycolate, povidone, sodium stearyl fumarate, opadry ii pink 85F540088 (polyvinyl alcohol, hydrolyzed, titanium dioxide, macrogol/peg, talc, iron oxide red, iron oxide yellow, ferrosoferric oxide/black, iron oxide), Purified water. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8^{th} in terms of function and quantities.

Manufacture

The finished product was manufactured at Hetero Labs Limited, Unit-V, TSIIC Formulation SEZ, S. No 439, 440,441 & 458, Polepally Village, Jadcherla, (Mandal), Mahaboob Nagar (District)-509301, Telangana State, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 14/02/2020.

Specifications

The FPP is non-compendia. The manufacturer controls the quality of the finished product as per in-house standards and ICH requirements. The parameters monitored during quality control are: description (visual), identity of dolutegravir (UV and HPLC), assay (HPLC), average weight (mass), uniformity of dosage (HPLC), dissolution (HPLC), water (KF), microbial enumeration tests, and test for specified microorganisms. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on three (3) batches of the finished product stored at 30^0 ± 2°C & 75% ± 5% RH for 36 months and 40^0 ± 2°C & 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 36 months when stored in HDPE bottle at Do not store above 30°C. Protect from moisture.

Safety and efficacy information

Hetero's Dolutegravir 50 tablets (dolutegravir sodium equivalent to dolutegravir 50 mg) is already registered by WHO. Information on clinical data has been fully evaluated during the registration of the product (Refer: WHO pre-qualification reference Number HA682). In this context, re-assessment of this part is not considered as necessarily required.

4. Benefit-Risk Assessment and Conclusion

On basis ofthe data submitted, the current state of knowledge and compliance to Good Manufacturing Practice, the benefit of the product outweighs the risks associated with its use when used in accordance to the summary of product characteristics. Dolutegravir is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response

Re-registration applications

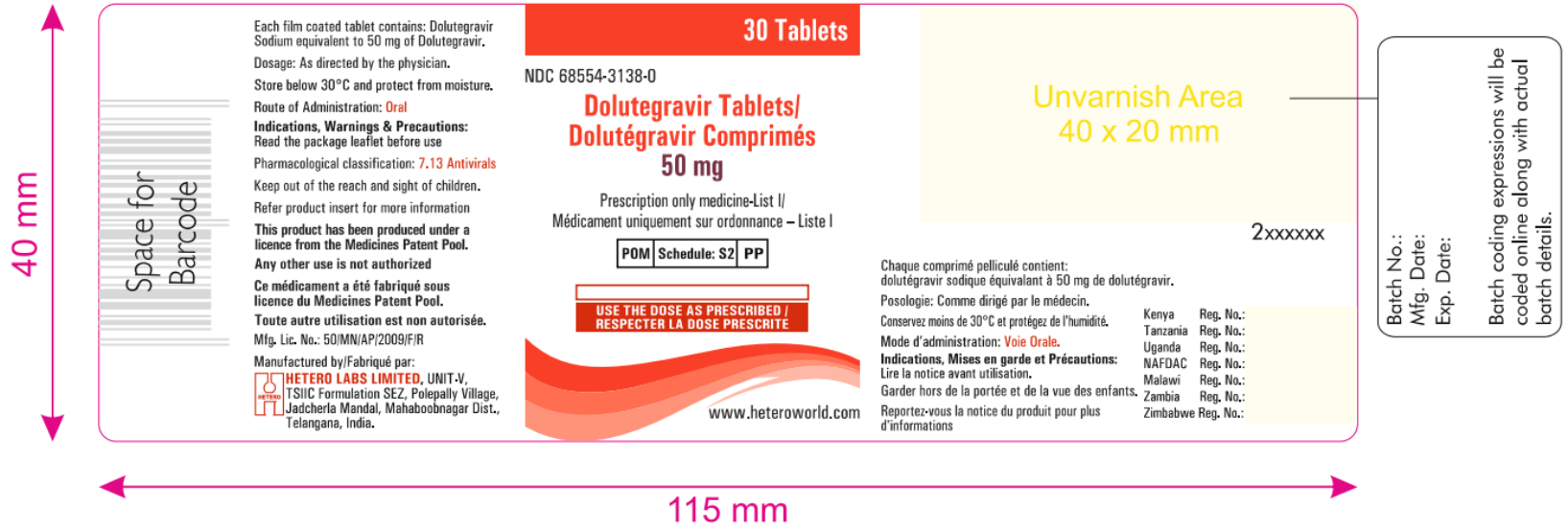
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

Version number	**Date**	**Description of update**	**Section(s) Modified**	**Approval date**

Annex I: Mock up label

Primary label:



Secondary label